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Dengue (with Notes on Yellow Fever and Japanese Encephalitis)

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Dengue, yellow fever, and the viral encephalitides (principally Japanese encephalitis) are acute, sometimes lethal infections which, with regard to morbidity and mortality, constitute the most significant arthropod-borne viral diseases of man. These viruses are all in the same taxon and share important biological similarities. Infections with wild or live-attenuated viruses result in lifelong immunity. Each virus is mosquito-transmitted and, therefore, typically causes diseases of place. Yellow fever and dengue share the same urban mosquito vector, *Aedes aegypti*; in some parts of Africa, related *Stegomyia* mosquitoes are more important for yellow fever transmission. Japanese encephalitis (JE) is transmitted by the rice-paddy breeding *Culex tritaeniorhynchus* and related species, which are distributed across the Asian land mass from Japan through India.

Arthropod-borne viral diseases are transmitted by injection of infected saliva during the bite of mosquitoes which, after ingesting blood containing virus, have survived sufficiently long for the virus to multiply in tissues, including the salivary gland. Following an incubation period in humans of a few days to a week or more, illness begins acutely, usually with fever, headache, myalgia, inappetence, and varying gastrointestinal symptoms. In its severe form, yellow fever evolves to an acute hepatitis, complicated by acute vascular permeability, hemorrhage, and renal failure; dengue evolves to dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), characterized by acute vascular permeability and bleeding. Japanese encephalitis involves acute central nervous system disease, commonly with altered cerebration, coma, and paralysis. In all three, the acute illness stage lasts for a week or more; severe findings and death or recovery occur promptly with yellow fever and DHF/DSS, but prolonged incapacitation is a frequent outcome of Japanese encephalitis.

Historically, case-fatality rates for yellow fever, dengue hemorrhagic fever, and Japanese encephalitis have been as high as 80 percent, 50 percent, and 60 percent, respectively. Today, in Africa, case-fatality rates for yellow fever are thought to be in the range of 0.5 to 6 percent; in tropical Asia, case-fatality rates for DHF/DSS are 1 to 5 percent; and in continental and South Asia, rates for Japanese encephalitis are 20 to 40 percent. Complication rates are extremely low for yellow fever and dengue, but for JE, long-term sequelae include personality disorders, reduced learning ability, gait abnormalities, and severe incapacitating paralysis. These occur in 25 to 40 percent of surviving patients.

In tropical Asia, DHF/DSS is almost exclusively confined to children under the age of fifteen years with a modal age of five to seven years. Male-to-female case and death ratios are approximately 1:1.2. Yellow fever epidemics in West Africa, Ethiopia, and Sudan have involved children and young adults with slightly more cases in males than females. Jungle yellow fever in Latin America involves principally young, adult males who work in or at the forest fringe. In China, under conditions of high enzootic transmission, Japanese encephalitis is a disease of children, principally five years of age and under; in Southeast Asia, an area of intermittent transmission, children up to fifteen years are vulnerable and, in South Asia, where virus is transmitted episodically, persons up to fifty years of age acquire encephalitis.

The primary risk factor for acquiring any of these diseases is living in areas where vector mosquitoes breed. Water storage in houses and promiscuous disposal of modern industrial trash permit *Aedes aegypti* breeding. *Culex tritaeniorhynchus* breeds in wet rice paddies. Children, females, Caucasians, and Orientals are the populations most at risk for DHF/DSS. There is no evidence to suggest that age, sex, or the innate susceptibility of blacks plays a part in the case-fatality rates of yellow fever. Japanese encephalitis is more severe and has higher case-fatality rates in children than adults and in Caucasians and blacks than Orientals.

In the remainder of this chapter we discuss all these conditions, describing their public health significance, economic effects, opportunities for better case management and prevention, and future priorities. We treat dengue in the greatest depth, presenting an empirical cost-effectiveness analysis. Dengue was selected for this more detailed analysis, and some original data were collected, because this condition poses the most difficult policy questions. Although there are current and prospective technologies with considerable potential to control the disease, their feasibility and cost in relation to the competing demands remains an open question.

Public Health Significance

Trends in the spread of epidemics and the levels of disability and death are the main public health concerns.

Morbidity and Mortality Levels and Trends, Circa 1985

Annually, jungle yellow fever is responsible for about 200 cases and 40 deaths in the tropics of the Western hemisphere, principally in adult males. Intermittent rural and urban epidemics occur in Sub-Saharan Africa (West, Central, and East). Much of African experience with yellow fever is unreported. During the 1987 Nigerian epidemic in Oyo State, 805 cases and 416 deaths were reported, but surveys of three involved villages suggested that as many as 120,000 cases and 24,000 deaths may have occurred (De Cock and others 1988). Another outbreak in the same year in Niger State in northern Nigeria may have been of similar dimensions (Nasidi and others 1989). Forty percent of cases were children under ten years; 30 percent were adults. The male-to-female ratio was 1.4:1. Yellow fever epidemics occur irregularly. The fifteen-year trend is toward increasing epidemic frequency, increasing involvement of urban areas in Nigeria, and extension to South Nigeria.

Attack rates of severe dengue illness have steadily increased. In 1987, more than 600,000 cases of dengue hemorrhagic fever with 24,000 deaths were reported from Southeast Asian countries. Ninety-nine percent of cases and deaths were in children under fifteen years. The male-to-female ratio is 1:1.2. In the Americas, dengue transmission has increased dramatically since 1963. There are four types of dengue, DEN 1, 2, 3, 4, and all four are now endemic in the Caribbean basin, and epidemic dengue has occurred in all South American countries except Argentina, Uruguay, and Chile. In 1981, DHF/DSS resulted in 116,000 hospitalizations in Cuba. Venezuela reported 50 deaths and 1,000 cases in a 1989–90 dengue outbreak, its first in many years (PAHO 1990). Brazil experienced thousands of cases in its first recent epidemic in 1986 (Schatzmayr and others 1986; Secretária de Estado de Saúde e Higiene 1986) and had a second resurgence in 1991. Attack rates in Southeast Asia have increased from 15 per 100,000 to 170 per 100,000 during the period 1970–87. In Thailand and Viet Nam, attack rates in 1987 were 3,700 and 6,400 per 100,000, respectively. Perhaps one-half of this increase is due to better case recognition and the fact that milder disease not reported earlier is now being reported (inflation of case identification). Nonetheless, cases reported are from medical facilities and signify use of diagnostic and curative services.

Cases of Japanese encephalitis have been reported in China, mainland Southeast Asia, and South Asia. Annual cases and deaths are estimated at 25,000 and 10,000, respectively, 70 percent in children below the age of fifteen years. The ratios of male-to-female cases and deaths are 1.1:1. There have been dramatic increases in epidemic occurrences of Japanese encephalitis in India, Nepal, Sri Lanka, and Thailand in the 1970s and 1980s. In this same period, JE has virtually disappeared from Japan, the Republic of Korea, and Taiwan (China) as a result of widespread use of effective vaccines. Annual cases in China have decreased from 100,000 to 25,000.

Morbidity and Mortality in 2000 and 2015

All three diseases are showing a tendency to increase absolutely with increasing population, but at a rate inversely proportionate to prosperity.

YELLOW FEVER. In Africa, there is increased risk of urban yellow fever transmitted by *Aedes aegypti*. For the past forty years, disease has predominantly affected rural areas, where it has been transmitted by other *Stegomyia* vectors. Attack rates and the area of involvement in Africa will increase with population and inversely with gross domestic product per capita.

DENGUE. Unless vaccine or nationwide vector control programs are implemented, the absolute number of cases of dengue will expand with population and growth of cities. Increases in gross domestic product per capita should reduce attack rates through improved standards for residential dwellings.

JAPANESE ENCEPHALITIS. Without incorporation of JE vaccine into the World Health Organization's (WHO's) Expanded Programme on Immunization (EPI) in South and Southeast Asia, attack rates will increase with population.

Economic Costs

Costs include those of treating the sufferers directly and the indirect social costs.

YELLOW FEVER. Yellow fever entails the same kinds of costs as those associated with dengue fever (see below): vector control, diagnosis and outpatient treatment of mild cases, and intensive care of the severely ill patients. Finally, there are costs associated with loss of work of adults ill themselves or attending children, and loss of life.

DENGUE. Costs include those associated with vector control, vaccination, diagnosis and outpatient treatment of mild cases (which are ten to fifty times more common than reported severe cases), and intensive care of the severely ill, including intravenous fluids, blood or plasma transfusion, and polypharmacy, with average hospital stays of five to ten days for severe cases. Adults lose work to attend to children's illness. Finally, there are costs associated with loss of life.

The literature contains no previous studies on the cost-effectiveness of dengue control. The literature on the economic consequences of dengue includes a study by Von

Allmen and others (1979) from Puerto Rico, in which the economic cost of the island's dengue fever epidemic of 1977 is calculated. Included are direct costs for medical care and vector control measures and indirect costs for lost production due to illness and absenteeism by patients and by parents caring for sick children. The population was 3 million. Direct costs ranged between $2.4 million and $4.7 million. Indirect costs ranged from $3.7 million to $10.9 million, with total costs of the epidemic ranging between $6.0 million and $15.6 million. Expenditure on patient care and vector control measures is considered to be in the range of 7.8 to 20.2 percent of the total expenses.

Gubler and others have also studied this epidemic and estimated costs to be an order of magnitude higher, ranging between $100 million and $150 million, in medical costs, control efforts, lost work, and lost tourism since 1977 (D. J. Gubler, personal communication 19 October 1992).

Kouri and others (1989) have estimated the cost of the 1981 DHF/DSS outbreak in Cuba (with a population of 10 million) at $103 million. In this outbreak more than 116,000 persons were hospitalized within a little over 3 months. It is remarkable that in such a short period more than 1 percent of the Cuban population required intensive care in a hospital setting. Included were direct costs for patient care and control of the vector of $41 million and $43 million, respectively, and indirect costs, including lost production of $14 million and disability payments of $5 million.

Much lower direct costs were estimated for the 1980 epidemic of DHF/DSS in Thailand, which included hospitalizations and deaths. Mosquito abatement costs and hospitalization costs, almost entirely for children, were $6.5 million (Matsurapas 1981; Halstead 1984).

Soper and others planned and executed with military-like precision environmental vector control in Brazil, and the efforts were replicated throughout the Americas (Soper and others 1943). Chan (1985) provides a thorough description, including a cost analysis, of the Singapore vector control program based on Soper's principles. The most important element of the program is source reduction—elimination of breeding sources for mosquitoes. Trained, uniformed public health officers are authorized to enter premises, inspect for, and destroy breeding sources. Destruction of breeding sources includes removing water-collecting refuse and sealing water storage containers. This environmental program is supplemented, in times of epidemics, by chemical control—fogging premises that have or are near places that have high *Aedes aegypti* indexes. Public health education, primarily through pamphlets, seeks to motivate and teach the population to eliminate breeding sites. During outbreaks, television, radio, and newspapers provide additional publicity. Moreover, Singapore enacted the Destruction of Disease-Bearing Insects Act (Act 26 of 1968) to require that persons comply with directives of the commissioner of health to eliminate breeding sources. Violations are punishable by fines. Chan reported that the environmental (*Aedes*) control program cost three to four Singapore dollars per person per year in 1973 to 1974, or $1.36 to $1.82 (Chan 1985). In 1988 prices, based on a 5 percent annual inflation, the amount is $2.69 to $3.60. In the early 1980s, following a dengue epidemic, Cuba also embarked on a program of environmental vector control at a total (not annual) cost of $6.00 to $10.00 per capita.

JAPANESE ENCEPHALITIS: The average hospital stay for persons with JE is two weeks. Forty percent of survivors are physically or mentally crippled and require one to five years rehabilitation; 10 percent of these require chronic care.

Prevention

Some measures can be taken immediately, others await improved technology.

Lowering or Postponing Disease Incidence

Elements of a preventive strategy are as follows:

YELLOW FEVER. Risk factors principally are overpopulation, rural to urban migration, vector prevalence, and inadequate domestic water supply or sewage disposal. There are two preventive strategies: (a) production, purchase, distribution, and use of yellow fever vaccine; and (b) control or eradication of *Aedes aegypti* (in Africa, limited to urban vectors). The potential effectiveness of either of these two strategies is 100 percent. The current price of yellow fever vaccine (excluding costs of administering the vaccine) is $0.20 to $2.00 per dose.

DENGUE. The strategy is the same as for yellow fever except vaccine development is in progress and outcome is not known. Dengue transmission can be interrupted by eliminating the mosquito vector (*Aedes aegypti* or *Aedes albopictus*) which carries the virus. Two methods are possible: chemical control—killing adult mosquitoes by means of chemical insecticides—and environmental control—elimination of sites for breeding of the mosquito which transmits dengue fever (Chan 1985). As Chan points out, the high fecundity of the mosquitoes means that they can quickly replace their population. Chemical control must be repeated several times per year and, even then, may be of limited effectiveness.

Environmental control, though more difficult, appears to be far more effective (Chan 1985). Rubbish, such as old tires, must be removed from the area; water storage vessels must be covered and cleaned regularly; and the presence of the mosquito must be diligently monitored. These activities require initial capital costs to set up an infrastructure, educate the population about control measures, establish rewards and sanctions for implementing them, and train the necessary environmental control personnel. Recurrent costs are the costs of operating this infrastructure.

We collected original data on the costs of vector control in several countries. Thailand launched a large-scale effort, which, so far, has been unsuccessful. The cost-effectiveness of this strategy will depend on the extent to which control efforts can be reduced following an initial success. Although good data are not yet available, we will attempt in this chapter to produce useful estimates.

One of the most important contributions to the eradication of the mosquito is the implementation of cleanup campaigns. Organized primarily by the national or city agencies, vector control requires community support. For example, in Puerto Rico, cleanup campaigns are organized for an urban neighborhood with a population of about 50,000 people. Cleanup campaigns start with large public education campaigns to raise awareness. These campaigns require the cooperation of the leaders of each community, who work directly with state and city officials. Householders agree to take responsibility for cleaning each premise. Special teams are formed for public areas (parks, cemeteries) and difficult places (slums and junkyards). City cleanup workers provide trash bags, cleaning utensils, and pick-up trucks to collect garbage. A neighborhood campaign generally requires two to three weeks of preparation and two to three days of trash removal activities.

In response to a dengue outbreak that peaked in June 1978, Puerto Rico began the Anti-Dengue Program with funds from the Comprehensive Employment and Training Act. From August 1978 through September 1980, the number of workers increased from 300 to 900 under the Higienización Ambiente Físico Inmediato program. The workers were paid the current minimum wage of $600 per month. Thus, the annual cost of salaries for the clean-up campaign was about $4.3 million, or $1.30 per capita.

JAPANESE ENCEPHALITIS. Vaccine is the only preventive strategy for combating Japanese encephalitis. The current regimen is three doses of killed, purified vaccine. Currently, it is given to children in Korea, China, Japan, and Taiwan (China). In South and Southeast Asia, the wholesale cost is $2.30 per dose; in Southeast Asia, for children living in JE enzootic areas, two doses are recommended. As yet, there is limited distribution in South and Southeast Asia.

Possible Changes in Preventive Technology

Some improvements in technology may be available by the year 2000, some not until 2015.

YELLOW FEVER. For yellow fever, an improved vaccine is not anticipated by the year 2000. Improvements in vaccine production technology and increased production in developing countries could reduce the price and improve efficiency at delivery.

DENGUE. For dengue, a safe and effective genetically engineered vaccine is not likely by the year 2000, but it is likely by 2015. To date, research on development of a vaccine has been performed in Thailand, supported principally by the Southeast Asia Regional Office of the World Health Organization in New Delhi, India. The planned live-attenuated tetravalent dengue vaccine is likely to have a manufacturing cost of at least $10 to $20 per dose and require refrigeration during shipment and storage. It will have a very short shelf-life once rehydrated from the lyophilized product. In this respect, it will be similar to yellow fever and measles vaccines.

Costs of the vaccine strategy include capital costs for vaccine development and operating costs for vaccine manufacturing and delivery. A tetravalent live-attenuated dengue vaccine will be expensive to produce, but delivery costs should not be excessive because the vaccine will require only two doses and will be given primarily in cities. In all likelihood, the first dose of dengue vaccine will be administered with measles vaccine and added to the existing infrastructure of the Expanded Programme on Immunization for children.

JAPANESE ENCEPHALITIS. For Japanese encephalitis, one or more live-attenuated vaccines are likely to be available by 2000; genetically engineered vaccines are also likely to be available. The reduction in cost of a genetically engineered vaccine as compared with a live-attenuated vaccine will be marginal, although a one-dose live-attenuated vaccine will greatly decrease delivery costs.

Good Practice and Actual Practice

Good practice is not always within reach financially, and actual practice may not always be effective.

YELLOW FEVER. Vaccine-induced antibody barrier is quite effective in preventing urban yellow fever in Latin America. In the seven or eight African countries in which it has been used, vaccination effectively controls yellow fever. Vector control in Africa is almost completely ineffectual.

DENGUE AND JAPANESE ENCEPHALITIS. Except for those in Cuba and Singapore, modern *Aedes aegypti* control programs to combat dengue are in disarray. In contrast, excellent vaccine programs to combat JE operate in Japan, Korea, and Taiwan (China), and a good program has been activated in China. No widespread use of vaccines exists in Southeast and South Asia.

How Much Should Reasonably Be Done?

No countries have had the opportunity to examine health investments in relation to projected costs to the economy of yellow fever, dengue, or Japanese encephalitis. Yellow fever and JE, which involve adults or result in prolonged incapacitation, respectively, tend to make headlines and create hysteria. This has been the principal reason for government action in the past. Fear, political pressure, and the technical capacity of the society for vaccine production or vector control have dictated the actions adopted.

It is likely that domestic production of JE vaccine in Thailand and India would result in purchase and use of the product, whereas continued dependence on imported vaccine will result in temporization in adopting a national vaccination policy. Eradication of *Aedes aegypti* throughout the entire Western hemisphere currently offers the only preventive strategy for control of dengue and yellow fever.

Case Management

This section discusses opportunities there may be for improvements in case management.

Dengue

Palliation is the objective of medical intervention of DHF/DSS, which is characterized by loss of fluids internally through leaky capillaries and occasionally, severe hemorrhaging. Intensive hospital care is required and can successfully reduce the case-fatality rates of DHF/DSS. Management of the leaky capillary syndrome is complicated. In some cases treatment with fluid or fluid and plasma is useful, in other cases whole blood. Incorrect treatment can lead to heart failure and a substantial risk of mortality. To improve case management and reduce case-fatality rates, fundamentally soundly educated physicians and nurses are required, modern state-of-the-art and reliable laboratory facilities are essential, and adequately functioning pharmacies and a safe and resourceful blood supply system are required. Resources involved are capital resources for training of personnel and rehabilitating facilities and equipment and subsequently for increased operating costs of the maintenance of these facilities and equipment. In addition, good managers are needed to ensure that the facilities, equipment, and personnel remain available at optimum preparedness. Realistic levels of turnover must be included.

Theoretically, such improvements in case management can be costed and analyzed as if they were dedicated solely to the treatment of DHF/DSS. That is, we could calculate the cost of an education program solely for DHF/DSS, the costs of strengthening of laboratories, pharmacies, and wards solely for this condition. In practice, such a program might be undertaken to strengthen case management for other infectious diseases and would entail training, rehabilitation of facilities, and the like for several infectious diseases simultaneously. The cost and effectiveness would be greater than for treatment of dengue, and economies of scale may be realized.

Yellow Fever and Japanese Encephalitis

Intensive hospital care is also required for yellow fever. For Japanese encephalitis, palliation is necessary in addition to intensive hospital care, which may be followed by prolonged physical rehabilitation or even institutionalization.

Cost-Effectiveness of Dengue Control

We look at different combinations of factors that may affect overall costs of dengue control.

Structure of the Model

In this section we seek to quantify the cost-effectiveness of dengue control over the long run in those areas of the world at risk of the disease. As mentioned above, currently two strategies are available to control this disease—improved case management and vector control. In the future, a third strategy—vaccinations—may also become available. As preventive strategies, vector control and vaccinations (if and when available) would reduce the incidence of disease and thus reduce both morbidity and mortality. Case management primarily reduces mortality, with a small benefit in morbidity.

Combinations of strategies are also possible. Case management may be combined with either chemical or environmental vector control. In addition, case management, vector control, or both may be combined with vaccinations (if and when a vaccine is available). The costs of vector control or vaccination are not affected by other strategies. The cost of case management, however, is reduced by the presence of one or more of the preventive programs because the costs of case management depend on the number of cases. Vector control or vaccinations reduce the number of cases.

The effectiveness of combinations were calculated according to the principle that each control strategy eliminates a certain proportion of the deaths still remaining after other strategies have been applied. That is, the effectiveness of a combination of strategies is the product of the effectiveness fractions of each.

Dengue Epidemiological Scenarios

Studies of the cost-effectiveness of disease control must begin with prognoses of evolution of disease in the absence of any control measure. For dengue, these prognoses vary widely, according to conditions for dengue transmission and previous population exposure to one or more dengue viruses. Four different epidemiologic scenarios are possible. They are listed below, in order of increasing severity.

- Endemic dengue fever, in which disease is relatively silent except for dengue fever in young adults. Children are seen in doctors' offices with mild fevers. The situation in Brazil in 1987 through 1989 and in Puerto Rico during the past decade illustrated this scenario.
- An epidemic of dengue fever occurring in a largely susceptible population. This results in high morbidity in adults, absenteeism, loss of tourism, some hospitalization, a handful of hemorrhagic cases, and deaths. Brazil's outbreak in 1986 illustrated this situation.
- An epidemic of DHF/DSS occurring for the first time. Such an epidemic results in high morbidity and mortality in children and adults. This is a one-time-only occurrence and not a stable state. Examples are the Cuban epidemic of 1981, in which half of deaths and cases were in children, and the Venezuelan epidemic of 1989–90.

- Endemic DHF/DSS. In this scenario there is continuous high morbidity and mortality, limited to children. The situation in Thailand is an illustration.

In establishing a potential scenario for calculating the costs of dengue, it seems most appropriate to choose the endemic steady state of DHF/DSS (the last of the four epidemiologic scenarios). This situation results when there is unlimited abundance of *Aedes aegypti*. It is the most extreme scenario and the one which control is designed to avoid. Because present evidence suggests that only tropical Asia and tropical America are at risk of DHF/DSS, this cost-effectiveness study is targeted to hypothetical populations in these regions. Operationally, we have defined these regions as all of Central and South America and the Caribbean, and South and Southeast Asia. The core part of these regions contains 2.22 billion people (420 million in the Americas and 1.8 billion in Asia east of Pakistan [World Bank 1990]).

The calculational procedure of the model is concerned with the aggregate population of a country at risk. In the analysis of the vaccination strategy, the fact that a vaccine confers benefit only to the extent that it is used is taken into consideraion. Thus, following a model developed to aid in the analysis of vaccination programs (Shepard and others 1986), we multiply the efficacy of the vaccine and the coverage to arrive at the effectiveness of a vaccination program. For the purposes of the model, "coverage" means the correct administration of a vaccine. Thus, the word incorporates factors of diagnostic accuracy, provider compliance, and patient compliance, which are treated separately in some other studies.

As with other cost-effectiveness studies in the Health Sector Priorities Review, the model applies to a hypothetical population of one million persons of all ages in a country at risk of dengue. The model first estimates baseline results for costs and health effects if no control strategy is applied. It then estimates results assuming individual or combined strategies are applied.

All economic data for the model are expressed in constant 1988 U.S. dollars. The model uses fully allocated costs, rather than marginal costs, for all inputs. This method is appropriate because costs are being considered over the long run in many countries; results are being used to inform policies that are concerned with the creation or dismantling of whole programs, in which marginal considerations may not apply. The data also need to be comparable with companion cost-effectiveness studies.

The main measure of health benefits are disability-adjusted life-years (DALYs) in the standard population of one million. This measure combines a loss in life expectancy and in quality of life as a result of dengue. Future costs and health benefits are both discounted at a rate of 3 percent per year.

Feasible Applications in Each Setting

In any meaningful application of the model, only potentially feasible interventions should be included. The designation of which interventions are potentially feasible depends on the country and time frame in which the application is set.

The country is important because the levels of development of the health delivery system vary widely among nations. For one of the interventions in the model, case management, benefits depend critically on the level of sophistication of the health delivery system. In this analysis, we have categorized the health delivery system as either "developed" or "not developed" (or unevenly developed). Developed systems are ones which meet five criteria: (a) most of the population has access to quality primary health services; (b) the population is sufficiently sensitized to acute problems such as dengue that a severely ill child will receive medical care within twelve hours; (c) personnel in primary and first-level referral facilities are sufficiently trained that they can generally stabilize an acute illness and refer a case for definitive care when needed; (d) an acutely ill child can reach a secondary health facility within twelve hours; and (e) referral facilities have the technical development, personnel, and equipment to perform current treatments safely and effectively. Health systems without this capacity are termed "not developed." Because of the level of development of the health system required to implement effective case management for dengue, this strategy has proved feasible only in countries with strong health delivery systems.

For example, improved strategies of case management have been implemented in Thailand during the past thirty years. During this period the case-fatality rate from dengue hemorrhagic fever has fallen from 5.8 percent in 1958–65 to 0.5 percent in 1986–89. In general, children are promptly referred in emergencies. Physicians with the equivalent of United States specialty training who have adequate laboratory back up are on duty in a pediatric intensive care unit twenty-four hours per day. Nursing staff are skilled in managing pediatric emergencies and inserting intravenous lines to rehydrate children in emergency with minimal risk of infection.

In other countries in southeast Asia, such as Myanmar, Cambodia, Lao People's Democratic Republic, and Indonesia, the overall level of development of the health delivery system does not meet the criteria we have listed above. Although a few centers provide excellent care, success with improved case management has not been achieved on a national scale. Although this discussion of applications is based on countries, future extensions of it could consider regional policies based on variations within a country.

A country's mortality rate of children under five years of age serves as a good proxy for the level of development of its health system. We would expect that most countries which the United Nations Children's Fund (UNICEF) characterizes as having "middle" or "low" under-five mortality rates (70 or less per 1,000 live births) would have strong health systems, whereas most countries with "high" or "very high" rates (greater than 70) probably have variable health systems. Thailand and Indonesia had under-five mortality rates of 34 and 97, respectively, as of 1990 (Grant 1992), so their rates are consistent with this classification.

The time frame of an application is important because it determines the status of vaccine development. We have characterized vaccine status as either "available" or "not available." As of 1992, dengue vaccines appear ready for final testing and development by a vaccine manufacturer. Nevertheless, no vaccine is currently available for general use. It is assumed in the "vaccine available" case that current development efforts are successfully completed and that a vaccine for mass use is available. If current efforts continue successfully, this would be about 1997.

Up to four single interventions are considered in this cost-effectiveness model:

- Case management improved (C)
- Immunization against dengue virus (I)
- Vector (the *Aedes aegypti* mosquito) chemically controlled (V)
- Environmental vector control (E)

Because the two types of vector control would be duplicative, they are considered exclusive. Otherwise the single interventions can be combined up to three at a time.

The combinations of development of the health delivery system and availability of vaccine create four settings or cases: no vaccine in a developed and in an undeveloped health system and available vaccine in a developed and in an undeveloped system. In table 14-1 we show the various policies available in each setting. Even in the most constrained setting (no vaccine in a developed system), more than one policy is available. In the most inclusive setting (vaccine available in an undeveloped system), ten choices are possible.

In the analysis of the cost-effectiveness of potentially feasible alternatives, we consider two criteria: dominance and relative cost-effectiveness. The dominance criterion means that some interventions or combinations can be eliminated in some settings because they are inferior to another intervention (or mixture of interventions) on both costs and effectiveness. The relative cost-effectiveness criterion indicates the important policy tradeoffs between resources allocated to dengue control and results. These concepts will be clarified and displayed graphically in the context of specific numerical results below.

To evaluate the alternative policies, a cost-effectiveness model was applied with the best available data from the literature; case studies in Puerto Rico and Brazil, and subjective estimates. The cost-effectiveness model is specified in detail in the three appendixes to this chapter.

Results

Using the model described above, we projected the results of applying each policy to a population of one million people. The results are expressed in the cost and benefits per year of application in figures 14-1 through 14-5. The benefits are expressed either in deaths averted or disability-adjusted life-years (DALYs) saved. Baseline data are for the absence of any control policy and are considered to be those with no costs and no health benefits. In table 14-2 we show the results for all the dengue control strategies. Here all the policies (both single and combination) are listed alphabetically, regardless of their feasibility in a particular setting.

Examination of the data in table 14-2 shows that the interventions in the combined policies interact nonlinearly. For example, the combination VC averts fewer deaths than the sum of V and C. The cost is also somewhat less than the sum of the costs. This is so because any preventive strategy, such as V, reduces the number of cases requiring treatment. Thus, the benefit and added costs from better treatment are both less than when there were more cases.

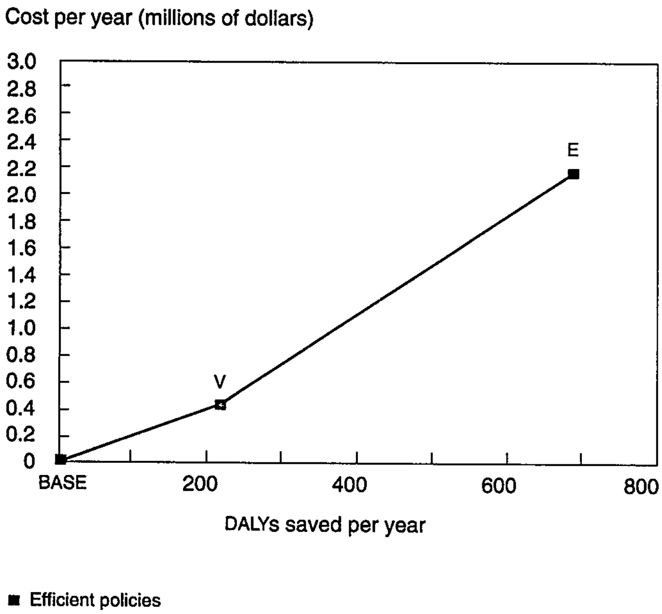
The results of applying the model in each of the four settings are shown in graphic form in figures 14-1 through 14-5. The main part of the analysis, summarized in the first four figures, presents the results in cost per disability-adjusted life-year. In these figures, each feasible policy (a single intervention or combination of interventions) is denoted by a square or a dot. The letters above the square or dot are the label for the policy, as described in table 14-2. All the figures begin with the baseline (no control), which entails zero cost and zero health benefits.

Table 14-1. Interventions for Dengue Control in Developed and Undeveloped Health Systems

Vaccine availability	*Developed health system*	*Undeveloped health system*
No vaccine	Vector chemically controlled (V) Environmental vector control (E)	Case management improved (C) Vector chemically controlled (V) Environmental vector control (E) Environmental control and case management (EC) Vector chemically controlled and case management (VC)
Vaccine available	Immunization (I) Vector chemically controlled (V) Environmental vector control (E) Immunization and vector chemically controlled (IV) Immunization and environmental control (IE)	Case management improved (C) Immunization (I) Vector chemically controlled (V) Environmental vector control (E) Environmental control and case management (EC) Vector chemically controlled and case management (VC) Immunization and case management (IC) Immunization and vector chemically controlled (IV) Immunization and environmental control (IE) Immunization, case management, and environmental control (ICE)

Source: Authors.

Figure 14-1. DALYs Saved without Vaccine Available in Undeveloped Health System
(per 1 million population)



Note: BASE = Baseline; *Efficient policies* : V = Vector chemically controlled, E = Environmental vector control.
Source: Authors' cost-effectiveness model

In calculating DALYs, each death averted was 25.5 discounted years, which becomes 25.5 DALYs. No quality adjustment was required for deaths, because if a person survives an episode of DHF/DSS, he or she will not have any long-term impairment. By comparison, the regular (undiscounted) life expectancy at age 6, calibrated to areas at risk of dengue, is 63.8 years.

In figure 14-1, only three policies are shown: BASE, V, and E. These are the only feasible policies in countries without a developed health system and without a vaccine available. The position of policy E at the right of the graph shows that it is the most effective of the feasible policies in this setting. The fact that it is also the highest on the vertical axis indicates that it is also the most costly policy. The slope of the line segment from the baseline to the first policy (V) corresponds to the cost-effectiveness of that policy, in average cost per DALY saved. According to table 14-2, this cost-effectiveness ratio is $1,992. It is the ratio of the net cost of that intervention (approximately $435,000) divided by its effectiveness (219 DALYs saved), also shown in table 14-2.

Chemical vector control is technically a more cost-effective policy than the alternative of environmental control, which costs $3,129 per DALY, because its cost-effectiveness ratio is lower. That is, a given amount of money can buy more DALYs if spent on V rather than E.

An ideal policy would fall in the lower right corner of this graph—substantial health benefits and minimal costs. A poor policy would lie in the upper left corner—few benefits but high costs. The frontier of current efficient policies, shown by the solid line, is obtained by connecting those currently available policies for which no other policy is closer to the lower right corner. Thus, the baseline, V, and E form the frontiers of current efficient policies.

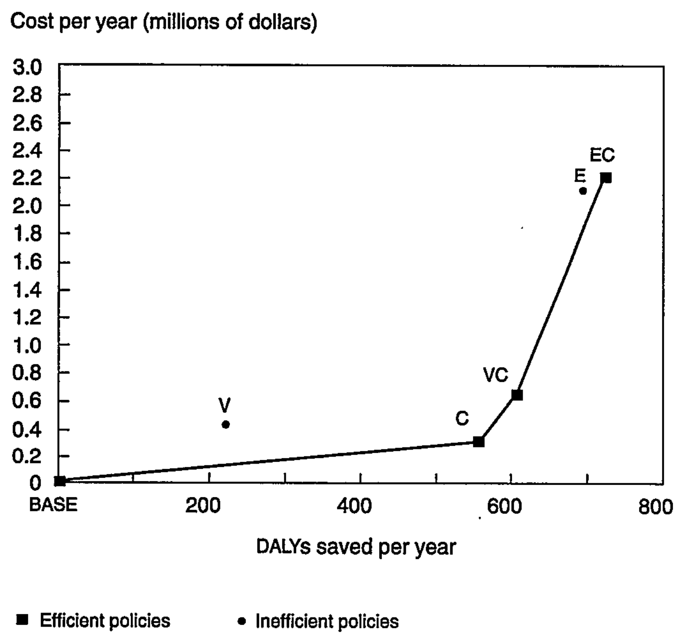
Figure 14-2 is an analogous graph for the situation in which no vaccine is available in a developed health system. Improvement in case management is a feasible intervention, both alone

Table 14-2. Efficacy and Costs of Interventions for Dengue
(per 1 million population)

Intervention	Deaths averted	DALYs saved from: Mortality	Morbidity	Total	Percent	Net cost ($000)	Average cost per DALY($)	Average cost per death ($)
Baseline (BASE)	0.00	0	0	0	0	0	0	0
Case management improved (C)	21.74	554	3	557	92	327	587	15,042
Environmental vector control (E)	22.52	574	118	692	95	2,172	3,139	96,461
Environmental control and case management (EC)	23.61	602	118	720	100	2,189	3,040	92,712
Immunization (I)	16.44	419	86	505	69	727	1,440	44,251
Immunization and case management (IC)	23.10	589	87	676	97	828	1,224	35,827
Immunization, case management, and environmental control (ICE)	23.68	604	123	727	100	2,959	4,071	124,968
Immunization, case management, and vector chemically controlled (ICV)	23.28	594	98	692	98	1,250	1,806	53,691
Immunization and environmental vector control (IE)	23.34	595	122	717	98	2,954	4,117	126,537
Immunization and vector chemically controlled (IV)	18.62	475	97	572	79	1,180	2,062	63,372
Vector chemically controlled (V)	7.11	181	37	219	30	435	1,992	61,234
Vector chemically controlled and case management (VC)	22.33	569	39	609	94	664	1,091	29,754

Source: Authors' cost-effectiveness model.

Figure 14-2. ***DALYs Saved without Vaccine Available in Developed Health System***
(per 1 million population)



Note: BASE = Baseline; *Efficient policies*: C = Case management improved, VC = Vector chemically controlled and case management, EC = Environmental control and case management; *Inefficient policies*: V = Vector chemically controlled, E = Environmental vector control.
Source: Authors' cost-effectiveness model

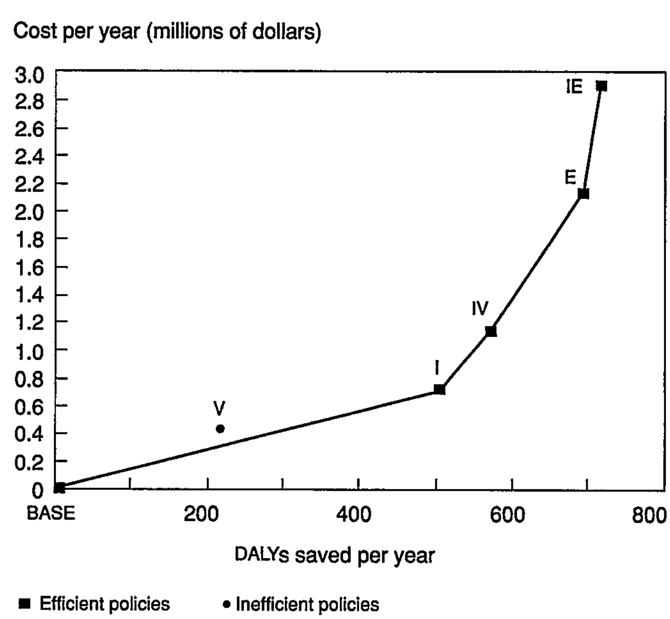
and combined with other interventions. The efficient policies (C, VC, and EC) are shown by squares. These results show that case management is now the most cost-effective policy. It saves one DALY for $587, about a third of the cost of achieving this benefit with policies V or E, respectively. Case management is also a powerful policy, being able to save 92 percent of the morbidity imposed by dengue in the cohort. It must be emphasized, however, that this seemingly attractive policy is feasible because of and is dependent on a developed health system.

Policymakers often face the choice between the most cost-effective policy and the most effective policy. In the case of dengue control, an efficient policy that would yield still greater benefits is a combination of chemical vector control and case management (VC). As shown in table 14-2, policy VC saves 609 DALYs, compared with 557 saved by policy C. At a cost of $1,091 per DALY, policy VC is somewhat less cost-effective than policy C. The next step in effectiveness is to replace chemical by environmental vector control as an addition to case management (policy EC). The number of DALYs gained by this policy (720) is virtually the entire burden of dengue, but the cost for the cohort of one million persons ($2,172,000) would be substantial.

Although policy V is still feasible in the case of no vaccine in an undeveloped health system, economically it is no longer efficient. A partial application of the case management strategy to part of the population of one million persons could achieve the same benefit in DALYs at a lower cost than policy V. In technical terms, a combination of BASE and C dominate policy V. This dominance is shown graphically by the fact that the line from BASE to C passes underneath the dot for policy V. In these figures, efficient strategies are shown by squares, whereas dominated policies are shown by dots. Strategy V is not economically efficient because this strategy was considered only 30 percent effective. Because the dengue-carrying mosquito breeds quickly, populations reduced by chemical spraying have been found to return quickly.

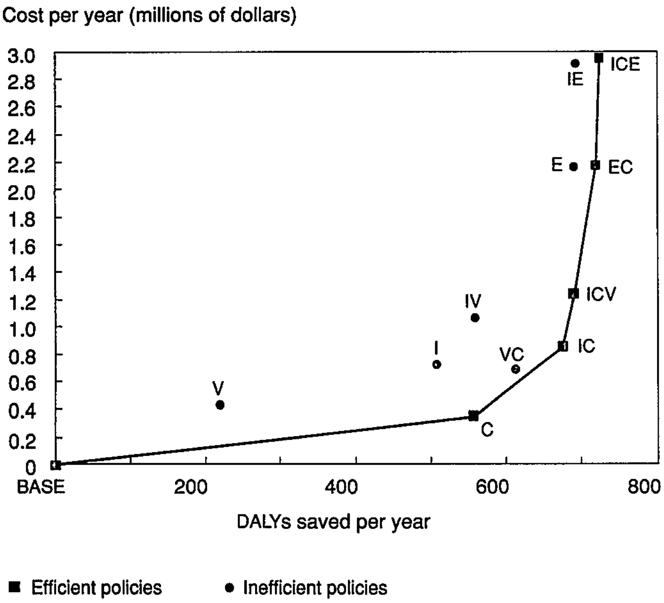
The technique of incremental cost-effectiveness analysis is useful to illustrate the tradeoff between cost-effective and effective policies. In table 14-3 we present this analysis in tabular form. The tradeoff is judged by the number of additional DALYs gained in relation to the additional cost incurred. The ratio of the additional cost to the additional gain in DALYs is the incremental cost-effectiveness ratio. For example, the comparison between policies VC and C show an incremental gain of fifty-one DALYs at an incremental cost of $337,000. The incremental cost-effectiveness ratio is $6,568, corresponding to approximately $337,000 per fifty-one DALYs. Graphically, this ratio corresponds to the slope of the line segment from C to VC. This line segment is substantially steeper than that from BASE to C, showing that the cost to save each of these few additional DALYs is quite high. In common parlance, it illustrates the decreasing marginal returns of larger investments in dengue control while holding the population fixed. Only efficient policies are listed in table 14-3, because they are the only ones to which incremental cost-effectiveness applies.

Figure 14-3. ***DALYs Saved with Vaccine in Undeveloped Health System***
(per 1 million population)



Note: BASE = Baseline; *Efficient policies*: I = Immunization, IVS = Immunization and vector chemically controlled, IE = Environmental vector control, E = Immunization and environmental control; *Inefficient policies*: V = Vector chemically controlled.
Source: Authors' cost-effectiveness model

Figure 14-4. DALYs *Saved with Vaccine in Developed Health System*



Note: BASE = Baseline; *Efficient policies:* C = Improved case management, IC = Vaccination and case management; ICV = Vaccination, case management, and vector chemically controlled, EC = Environmental vector control and case management, ICE = Vaccination, case management, and environmental vector control; *Inefficient policies:* V = Vector chemically controlled, I = Immunization, VC = Vector chemically controlled and case management, IV = Immunization and vector chemically controlled, E = Environmental vector control, IE = Immunization and environmental control.
Source: Authors' cost-effectiveness model

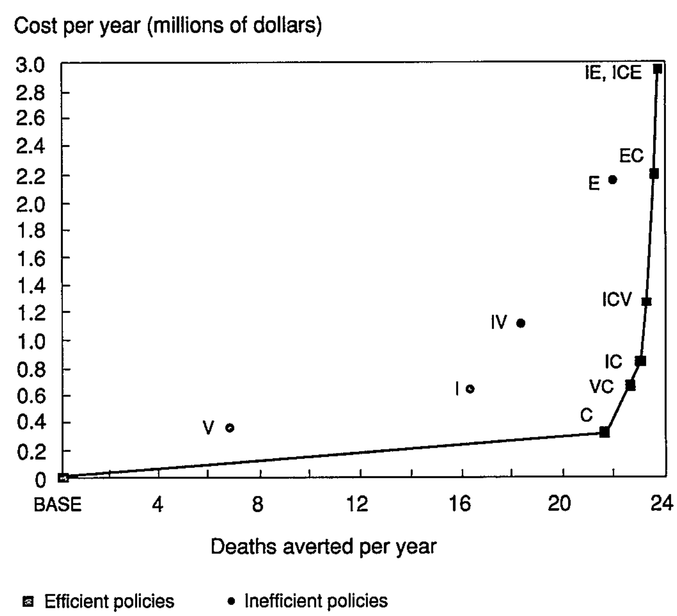
Figure 14-3 introduces the case in which a dengue vaccine is available, but the health system is still not developed. As explained in the appendix 14C, a dengue vaccine is expected to be 95 percent effective in protecting persons who receive it. In a population, however, its effectiveness is limited by a coverage of only 73 percent, the rate obtained for the third dose of DPT according to 1990 UNICEF data. As of 1992, a vaccine is expected to be available in three to five years, assuming the final development continues as planned. For this analysis, we have taken the longer estimate, giving a target date of 1997. Immunization is the most cost-effective strategy, followed by IV, E, and IE. Again, strategy V is not economically efficient. The incremental cost-effectiveness analysis comparing policies E and IE shows that adding immunization onto environmental control is not particularly cost-effective. The incremental cost per DALY gained is $30,927.

In figure 14-4, we present the analysis for the case in which the full range of alternatives is available. A vaccine is available and the health system is developed. Again, case management is the most cost-effective strategy. It is interesting that none of the preventive single interventions—immunization, chemical vector control, or environmental vector control—was economically efficient alone. Each was dominated by a combination of strategies that include case management. The immunization result is because of the relatively high cost of immunization of $40.87 per person; the cost is a result of the assumed high cost of the vaccine itself ($17.50 per dose) and the need for two doses. The relatively high cost of vector control arises because vector control must be practiced for the entire population every year, whereas case management affects only sick patients.

A sensitivity analysis for vaccination showed immunization would become as cost-effective as case management if the cost of the series were to drop to $18.00. Allowing $3.07 (in future value) for the two vaccination contacts, as assumed in the base case, this would leave about $7.00 per dose for the vaccine itself. The dramatic drop in the price of hepatitis B vaccine illustrates that such a drop is possible. Initially introduced at a prohibitive price of $100.00 per dose, a plasma-derived hepatitis B vaccine is now available for only $1.00 per dose for bulk purchase by developing countries. A sensitivity analysis on case management showed that if the base cost of hospitalization episode (TREAT) rose from $200.00 to only $438.00, it would no longer be the most cost-effective strategy.

The analysis for the case in which vaccine is available in a developed health care system was also calculated in cost per death averted, as shown in figure 14-5. Although the numbers change, the demarcation between dominated and efficient policies, and the ordering among the efficient policies remains the same. The advantage of policy C over policy I in cost-effectiveness is seen more dramatically in deaths averted,

Figure 14-5. Deaths Averted with Vaccine in Developed Health System
(per 1 million population)



Note: BASE = Baseline; *Efficient policies* : C = Improved case management, VC = Vector chemically controlled and case management, IC = Vaccination and case management; ICV = Vaccination, case management, and vector chemically controlled, EC = Environmental vector control and case management, ICE = Vaccination, case management, and environmental vector control; *Inefficient policies:* V = Vector chemically controlled, I = Immunization, IV = Immunization and vector chemically controlled, E = Environmental vector control, IE = Immunization and environmental control.
Source: Authors' cost-effectiveness model

Table 14-3. Incremental Cost-Effectiveness of Interventions for Dengue Control

Intervention	*DALYs saved*	*Net cost ($000)*	*Average cost per DALY ($)*	*Average cost per death ($)*	*Additional DALYs gained*	*Additional cost ($000)*	*Incremental cost per DALY ($)*
No vaccine and health system not developed							
Baseline (BASE)	0	0	0	0	0	0	0
Vector chemically controlled (V)	219	435	1,992	61,234	219	435	1,992
Environmental vector control (E)	692	2,172	3,139	96,461	474	1,737	3,668
No vaccine but developed health system							
Baseline	0	0	0	0	0	0	0
Case management improved (C)	557	327	587	15,042	557	327	587
Vector chemically controlled and case management (VC)	609	664	1,091	29,754	51	337	6,568
Environmental control and case management (EC)	720	2,189	3,040	92,712	111	1,524	13,696
With vaccine but health system not developed							
Baseline (BASE)	0	0	0	0	0	0	0
Immunization (I)	505	727	1,440	44,251	505	727	1,440
Immunization and vector chemically controlled (IV)	572	1,180	2,062	63,372	67	452	6,754
Environmental vector control (E)	692	2,172	3,139	96,461	120	992	8,278
Immunization and environmental control (IE)	717	2,954	4,117	126,537	25	781	30,927
With vaccine and developed health system							
Baseline (BASE)	0	0	0	0	0	0	0
Case management improved (C)	557	327	587	15,042	557	327	587
Immunization and case management (IC)	676	828	1,224	35,827	119	501	4,217
Immunization, case management, and vector chemically controlled (ICV)	692	1,250	1,806	53,691	16	422	26,363
Environmental control and case management (EC)	720	2,189	3,040	92,712	28	939	33,643
Immunization, case management, and environmental control (ICE)	727	2,959	4,071	124,968	7	770	112,933

Note: Only policies that are feasible and economically efficient are listed.
Source: Authors' cost-effectiveness model.

because the number of deaths averted does not count the morbidity avoided by vaccinations.

Under both criteria, deaths averted and DALYs, case management remains the most cost-effective first strategy. The cost per DALY gained, $587, is comparable to the per capita income of an average low-income developing country. Thus, case management of dengue fever, although not as cost-effective as some of the other interventions examined in this collection, is still reasonable and cost-effective for all but the very poorest country. The cost per death averted, $15,042, is also an acceptable investment for a middle-income country. Among the preventive interventions, immunization, at $1,440 per DALY gained, is the most cost-effective policy.

Finally, the analysis adds future interventions to those under consideration. Case management remains the most cost-effective program, but the next intervention is to add immunization to case management (IC). That is, we first make sure treatment facilities can do a good job; then we add the preventive component. These results are opposite to the usual adage that prevention is cheaper than cure. With case management, we have a good argument for cure. Prevention is expensive and is directed to a condition that is relatively rare when both epidemic and nonepidemic years are averaged.

Priorities

On the basis of our analysis, we recommend policies in two areas. First, applying existing knowledge, we recommend measures for cost-effective control of dengue. Second, we examine how operational research could allow better disease control in the future.

Priorities for Resource Allocation

Policies differ among the three mosquito-borne diseases. For the two for which effective vaccines are available (yellow fever and Japanese encephalitis) the major questions concern overcoming the technical and financial constraints to vaccination.

DENGUE. Policies for dengue control vary with time and the level of development of a country's health system. In the case in which no vaccine is available and the health system is not developed, chemical vector control was most cost-effective ($1,992.00 per DALY), although not very effective in an absolute sense. Environmental vector control, through reduction of breeding sites, is the only other alternative. As practiced in Singapore, this policy proved highly effective but somewhat costly ($2.25 per person per year, even after excluding costs for controlling nuisance mosquitoes). It would be highly effective, and only slightly less favorable on cost-effectiveness than controlling mosquitoes through spraying.

In the case in which no vaccine is available but the health system is developed, the cost-effectiveness analysis suggests that case management is the most cost-effective policy ($587 per DALY). The analysis suggests that this method should be undertaken first. For additional control, chemical or environmental vector control should be added.

In the case in which a dengue vaccine is assumed to be available (beginning in 1997) but a country's health system is not developed, immunization would be the most cost-effective alternative at $1,440 per DALY. In the model, we estimated a relatively high cost for the assumed two-dose series for this vaccine of $40.87 per person vaccinated. If this price dropped with increasing volume, the cost-effectiveness of this option could improve substantially. For example, if the price per dose of vaccine dropped from its assumed value of $17.50 to $7.00, then immuniztion would become as cost-effective as case management.

In the case in which a dengue vaccine is available and the health system is developed, all policies would be technically feasible. Case management proved to be most cost-effective at a cost per DALY of $587, but immunization would be a valuable addition at an incremental cost of $4,217 per additional DALY gained. Case management and vaccination would be expensive for the countries with the lowest income. Many countries at risk of dengue in Asia and South America are middle- or upper-middle-income countries. For them, dengue control is a reasonable part of their health priorities.

An important caveat is that our analysis of vector control captures only direct patient benefits. Thus, certain secondary benefits of vector control are not captured or are incompletely measured. They include reduction in the nuisance and discomfort of mosquito bites, possible reduction in transmission from fewer infected people, and a possible reduction in the risk of other vector-borne diseases, such as yellow fever. The impact on yellow fever would be only a theoretical advantage in most regions of the world, however. The other, less tangible benefits, cannot be valued within the scope of this chapter.

Although a thorough sensitivity analysis has not been done, the cost-effectiveness of case management depends on the availability of moderately priced, high-quality referral hospital care. We assumed that the base cost of treating DHF/DSS was $200 per case (for an average hospital stay of five days) and that improved case management would raise this cost fivefold. If the base cost were about twice as high ($487 per case), the cost-effectiveness of case management would then be equal to that of vaccinations.

One factor in favor of each of these control programs is that they can be implemented on localized scales. Improvements in case management could be implemented at a single hospital. Vector control, whether chemical or environmental, could be implemented at the level of a single city, and in part, at a neighborhood level. The delivery of a vaccine, once it has been developed, can be directed to receptive populations. Thus, although the cost-effectiveness of dengue control policies may not place them in the highest priority for low-income countries, they certainly are feasible for middle-income countries and particularly for middle-class populations within middle-income countries.

Finally, the choice between preventive and curative policies involves ethical issues. Some public health officials feel that a society has an obligation to prevent disease if it can reasonably do so, even if curative policies appear somewhat more cost-effective in the short run. The public's willingness to undertake future preventive measures would be an additional benefit.

YELLOW FEVER. Partly because of its high case-fatality rate and partly because yellow fever has been controlled on a hemispheric basis both by vector control and by vaccination, modern societies regard epidemics of yellow fever as intolerable. In Africa, adequate supplies of potent yellow fever vaccine must be on hand for preventive immunization programs and to combat yellow fever epidemics. Nigeria, repeatedly affected by epidemics, still depends heavily on an antiquated manufacturing facility established by the Rockefeller Foundation in 1939. It is quite possible that batches of this vaccine have relatively poor thermostability compared with those produced by other manufacturers and that they still contain avian leukosis virus. Some lots may be contaminated with other organisms. Nigeria and other African countries also import vaccine from Brazil, Senegal, and France. Even potent yellow fever vaccine is extremêly dependent upon an intact cold chain; on adequate supplies of jet injectors, needles, and syringes; and on trained vaccinators. All are at present inadequate. The authors recommend the following steps to address these problems:

- Funds should be made available to purchase and stockpile potent yellow fever vaccine.
- An effective delivery system is needed. Success in building a sustainable delivery system for EPI will also permit routine or emergency delivery of yellow fever vaccine.
- Yellow fever vaccine should be incorporated into the EPI program for those countries in Africa at risk of yellow fever.

JAPANESE ENCEPHALITIS. Public outcries and political pressures for action seem to be particularly powerful against this disease. Nonetheless, many affected nations have postponed the purchase of sufficient quantities of vaccines needed to immunize all at-risk children. This is largely because of the high cost in hard currency of Japanese-manufactured killed vaccines (at least $4.60 to $6.90 just for vaccine alone). India and Thailand, with Japanese assistance, are investing in domestic vaccine manufacturing facilities. These will require huge colonies of laboratory mice. There is reason to doubt, based on past performance, that output of vaccine will be sufficient for national needs. Estimates of current and projected costs and losses resulting from Japanese encephalitis might contribute to rational investment policies, whether for domestic manufacture or for vaccine importation.

Priorities for Operational Research

Priorities for operational research focus on ways to control the mosquito, development of vaccine (for dengue) improvement of vaccines (for yellow fever and Japanese encephalitis).

DENGUE. First, careers in vector control need to be entirely reconstituted. The leaders and experienced veterans of the Latin American *Aedes aegypti* campaigns have disappeared without replacements. Second, politically acceptable, cost-effective methods of *Aedes aegypti* control or eradication are needed. Third, research on cost-effective, efficacious, safe, and thermally stable vaccines requires adequate funding. Current programs are very poorly funded.

YELLOW FEVER. A second-generation genetically engineered vaccine might overcome the present requirement for lyophilization.

JAPANESE ENCEPHALITIS. First, a potent, safe, thermally stable live-attenuated vaccine is needed. A reasonable candidate has been developed in China. This requires internationally acceptable phase I, II, and III testing and introduction into the affected countries of Thailand, Myanmar, Nepal, Bangladesh, India, and Sri Lanka. Second, investments, both technical and financial, are needed in vaccine production capacities in most of these affected countries.

Appendix 14A. Definitions of Variables in the Cost-Effectiveness Model

The model involves the following parameters:

Morbidity and mortality

STAND.POP: The number of persons in the standard population (an arbitrary size) to which the model is applied. Here STAND.POP is one million persons of all ages.

CASES: Number of dengue infections without vaccination or vector control in the hypothetical birth cohort (all births within the standard population in one year).

SHOCK.R (Shock rate): Proportion of dengue infections that progress to dengue shock syndrome.

FATAL: Case-fatality rate of DSS 1960–65.

CLINICAL: Proportion of dengue infections which are clinically apparent.

DUR: Average duration of clinical illness, expressed in disability-adjusted life-years.

COHORT: Number of persons in one year's birth cohort in the standard population.

Effectiveness of interventions

YEAR.D: Discounted remaining life expectancy of a person at the average age of death of a fatal dengue case.

SALVAGE: Proportional reduction in case-fatality rate of DHF/DSS after improved case management.

SHORTEN: Proportional reduction in duration of illness among hospitalized cases after improved case management.

VACC.EF (vaccine efficacy): Proportional reduction in number of cases.

COVERAGE: Proportion of birth cohort vaccinated.

VCTRC.EF: (vector chemical efficacy): Proportional reduction in number of cases from chemical vector control.

VCTRE.EF: (vector environmental efficacy): Proportional reduction in number of cases from environmental vector control.

Costs of case management

TREAT: Current cost per case of treating hospitalized DHF/DSS.

IMPROVE: Cost as a multiple of TREAT per case of DHF/DSS of improved case management, converted to future value as of the average expected age at death from dengue.

Costs of vaccines

DEVELOP: Annualized expected development cost for cohort until successful development.

VACCINE: Vaccination cost per person vaccinated, converted to future value as of the average age at death from dengue.

Costs of vector control

VECTORC: Cost per person per year in target population of chemical vector control, including amortization of initial costs.

VECTORE: Cost per person per year in target population of environmental vector control, including amortization of initial costs.

The model also uses the following intermediate variables:

DEATHS: Number of dengue deaths in the standard population in one year with a specified control program.

D.AVERTED: The number of deaths averted in the standard population in one year.

D.BASELINE: The number of dengue deaths in the baseline situation of no dengue control program.

DALY.MORB: The number of disability-adjusted life-years saved through morbidity averted.

DALY.MORT: The number of disability-adjusted life-years saved through mortality averted.

YEAR.D: The discounted life expectancy at the average age at which one otherwise would have died of dengue.

Appendix 14B. Relationships in the Cost-Effectiveness Model

We look at these relationships in the context of deaths averted, disability-adjusted life-years saved, and aggregate costs.

Deaths Averted

The number of deaths is expressed as the product of the three factors: the number of infections times the proportion of those infections which progress to the potentially fatal condition of DHF/DSS times the proportion of DHF/DSS cases which are fatal. For consistency with the formulas in the computer spreadsheet in which this model was written, multiplication is shown by an asterisk. The equations below show how this principle applies to each of the control strategies.

Single interventions
At the baseline (policy BASE):

D.BASELINE = CASES · SHOCK.R · FATAL.

With case management improved (policy C):

DEATHS = CASES · SHOCK.R · FATAL · (1 – SALVAGE).

With immunization or vaccination (policy I):

DEATHS = CASES · (1 – VACC.EF · COVERAGE) · SHOCK.R · FATAL.

With vector chemically controlled (policy V):

DEATHS = CASES · (1 – VCTRC.EF) · SHOCK.R · FATAL.

With environmental vector control (policy E):

DEATHS = CASES · (1 – VCTRE.EF) · SHOCK.R · FATAL.

Two-way combinations
With vaccination and case management (policy IC):

DEATHS = CASES · (1 – VACC.EF · COVERAGE) · SHOCK.R · (1 – SALVAGE) · FATAL.

With vector chemically controlled and case management (policy VC):

DEATHS = CASES · (1 – VCTRC.EF) · SHOCK.R · (1 – SALVAGE) · FATAL.

With environmental vector control and case management (policy EC):

DEATHS = CASES · (1 – VCTRC.EF) · SHOCK.R · (1 – SALVAGE) · FATAL.

With immunization and vector chemically controlled (policy IV):

DEATHS = CASES · (1 – VACC.EF · COVERAGE) · (1 – VCTRC.EF) · SHOCK.R · FATAL.

With immunization and environmental vector control (policy IE):

DEATHS = CASES · (1 – VACC.EF · COVERAGE) · (1 – VCTRC.EF) · SHOCK.R · FATAL.

Three-way combinations
With immunization, case management improved, and vector chemically controlled (policy ICV):

DEATHS = CASES · (1 – VACC.EF · COVERAGE) · (1 – VCTRC.EF) · SHOCK.R · (1 – SALVAGE) · FATAL.

With immunization, case management improved, and environmental vector control (policy ICE):

DEATHS = CASES · (1 – VACC.EF · COVERAGE) · (1 – VCTRC.EF) · SHOCK.R · (1 – SALVAGE) · FATAL.

Number of deaths averted
For each strategy, the number of deaths averted is

D.AVERTED = D.BASELINE – DEATHS.

DALYs Saved

The number of disability-adjusted life-years saved with each policy is the sum of the number saved through deaths averted and through morbidity avoided or reduced. That is, for all interventions, the overall number of DALYs saved is

DALY.MORT + DALY.MORB.

The prevention strategies (vector control and vaccination) avoid morbidity, whereas case management shortens the morbidity of serious cases. The DALYs saved through deaths averted are

DALY.MORT = D.AVERTED · YEAR.D.

On the basis of experiences in Thailand (Halstead 1980b), the number of cases hospitalized is assumed to be twice the number experiencing dengue hemorrhagic shock or dengue shock syndrome.

Single interventions
Because case management benefits only hospitalized cases, only these cases experience a reduction in morbidity. The number of DALYs saved through shortened morbidity in case management (policy C) is

DALY.MORB = CASES · 2 · SHOCK.R · SHORTEN · DUR.

Infections with dengue virus, like some other infections, are not always clinically apparent. The benefit of reduced morbidity applies, of course, only to clinically apparent cases. For chemical vector control (policy V), the morbidity avoided is

DALY.MORB = CLINICAL · CASES · VCTRC.EF · DUR.

Similarly, for environmental vector control (policy E), the morbidity avoided is

DALY.MORB = CLINICAL · CASES · VCTRC.EF · DUR.

Immunizations are assumed to lower the attack rate of dengue but not to affect the severity of a dengue infection. Thus, for immunizations (policy I) the morbidity avoided is

DALY.MORB = CLINICAL · CASES · VACC.EF · COVERAGE · DUR.

Two-way combinations
When chemical or environmental vector control and case

management are combined, the benefits from cases avoided are supplemented by shorter morbidity for the hospitalized cases among those that still occur. The morbidity avoided from chemical vector control combined with better case management (policy VC) is

$$\text{DALY.MORB} = \text{CLINICAL} \cdot \text{CASES} \cdot \text{VCTRC.EF} \cdot \text{DUR} + \text{CASES} \cdot (1 - \text{VCTRC.EF}) \cdot 2 \cdot \text{SHOCK.R} \cdot \text{SHORTEN} \cdot \text{DUR}.$$

Similarly, the morbidity avoided from environmental vector control combined with better case management (policy EC) is

$$\text{DALY.MORB} = \text{CLINICAL} \cdot \text{CASES} \cdot \text{VCTRC.EF} \cdot \text{DUR} + \text{CASES} \cdot (1 - \text{VCTRC.EF}) \cdot 2 \cdot \text{SHOCK.R} \cdot \text{SHORTEN} \cdot \text{DUR}.$$

With immunization and the vector chemically controlled (policy IV) the morbidity avoided is

$$\text{DALY.MORB} = \text{CLINICAL} \cdot \text{CASES} \cdot \text{VCTRC.EF} \cdot \text{DUR} + \text{CASES} \cdot (1 - \text{VCTRC.EF}) \cdot \text{VACC.EF} \cdot \text{COVERAGE} \cdot \text{DUR}.$$

With immunization and environmental vector control (policy IE) the morbidity avoided is

$$\text{DALY.MORB} = \text{CLINICAL} \cdot \text{CASES} \cdot \text{VCTRC.EF} \cdot \text{DUR} + \text{CASES} \cdot (1 - \text{VCTRC.EF}) \cdot \text{VACC.EF} \cdot \text{COVERAGE} \cdot \text{DUR}.$$

With both vaccination and case management (policy IC), the morbidity avoided would be

$$\text{DALY.MORB} = \text{CLINICAL} \cdot \text{CASES} \cdot \text{VACC.EF} \cdot \text{COVERAGE} \cdot \text{DUR} + \text{CASES} \cdot (1 - \text{VACC.EF} \cdot \text{COVERAGE}) \cdot 2 \cdot \text{SHOCK.R} \cdot \text{SHORTEN} \cdot \text{DUR}.$$

Three-way combinations

With immunization, case management improved, and vector chemically controlled (policy ICV):

$$\text{DALY.MORB} = \text{CLINICAL} \cdot \text{CASES} \cdot (\text{VACC.EF} \cdot \text{COVERAGE} + \text{VCTRC.EF} - \text{VACC.EF} \cdot \text{COVERAGE} \cdot \text{VCTRC.EF}) \cdot \text{DUR} + \text{CASES} \cdot (1 - \text{VACC.EF} \cdot \text{COVERAGE}) \cdot 2 \cdot \text{SHOCK.R} \cdot \text{SHORTEN} \cdot \text{DUR}.$$

With immunization, case management improved, and environmental vector control (policy ICE):

$$\text{DALY.MORB} = \text{CLINICAL} \cdot \text{CASES} \cdot (\text{VACC.EF} \cdot \text{COVERAGE} + \text{VCTRC.EF} - \text{VACC.EF} \cdot \text{COVERAGE} \cdot \text{VCTRC.EF}) \cdot \text{DUR} + \text{CASES} \cdot (1 - \text{VACC.EF} \cdot \text{COVERAGE}) \cdot 2 \cdot \text{SHOCK.R} \cdot \text{SHORTEN} \cdot \text{DUR}.$$

Aggregate Costs

The aggregate costs are expressed as the number of people in the standard population receiving each service times the unit cost of that service.

Single interventions

Baseline (policy BASE):

$$\text{COSTS} = \text{CASES} \cdot \text{SHOCK.R} \cdot \text{TREAT}.$$

With improved case management (policy C):

$$\text{COSTS} = \text{CASES} \cdot \text{SHOCK.R} \cdot \text{TREAT} \cdot \text{IMPROVE}.$$

With vaccination (policy I):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VACC.EF} \cdot \text{COVERAGE}) \cdot \text{SHOCK.R} \cdot \text{TREAT} + \text{DEVELOP} + \text{VACCINE} \cdot \text{COVERAGE} \cdot \text{COHORT}.$$

With vector chemically controlled (policy V):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VCTRC.EF}) \cdot \text{SHOCK.R} \cdot \text{TREAT} + \text{STAND.POP} \cdot \text{VECTORC}.$$

With environmental vector control (policy E):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VCTRC.EF}) \cdot \text{SHOCK.R} \cdot \text{TREAT} + \text{STAND.POP} \cdot \text{VECTORE}.$$

Two-way combinations

With vaccination and case management (policy IC):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VACC.EF} \cdot \text{COVERAGE}) \cdot \text{SHOCK.R} \cdot \text{TREAT} \cdot \text{IMPROVE} + \text{DEVELOP} + \text{VACCINE} \cdot \text{COVERAGE} \cdot \text{COHORT}.$$

With vector chemically controlled and case management (policy VC):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VCTRC.EF}) \cdot \text{SHOCK.R} \cdot \text{TREAT} \cdot \text{IMPROVE} + \text{VECTORC} \cdot \text{STAND.POP}.$$

With environmental vector control and case management (policy EC):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VCTRC.EF}) \cdot \text{SHOCK.R} \cdot \text{TREAT} \cdot \text{IMPROVE} + \text{VECTORE} \cdot \text{STAND.POP}.$$

With vaccination and environmental vector control (policy IE):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VACC.EF} \cdot \text{COVERAGE}) \cdot (\text{VCTRC.EF}) \cdot \text{SHOCK.R} \cdot \text{TREAT} + \text{DEVELOP} + \text{VACCINE} \cdot \text{COVERAGE} \cdot \text{COHORT} + \text{STAND.POP} \cdot \text{VECTOR}.$$

With immunization and vector chemically controlled (policy IV):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VACC.EF} \cdot \text{COVERAGE}) \cdot (\text{VCTRC.EF}) \cdot \text{SHOCK.R} \cdot \text{TREAT} + \text{DEVELOP} + \text{VACCINE} \cdot \text{COVERAGE} \cdot \text{COHORT} + \text{STAND.POP} \cdot \text{VECTOR}.$$

Three-way combinations

With vaccination, case management, and vector chemically control (policy ICV):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VACC.EF} \cdot \text{COVERAGE}) \cdot (1 - \text{VCTRC.EF}) \cdot \text{SHOCK.R} \cdot \text{TREAT} \cdot \text{IMPROVE} + \text{DEVELOP} + \text{VACCINE} \cdot \text{COVERAGE} \cdot \text{COHORT} + \text{STAND.POP} \cdot \text{VECTORC}.$$

With vaccination, case management, and environmental vector control (policy ICE):

$$\text{COSTS} = \text{CASES} \cdot (1 - \text{VACC.EF} \cdot \text{COVERAGE}) \cdot (1 - \text{VCTRC.EF}) \cdot \text{SHOCK.R} \cdot \text{TREAT} \cdot \text{IMPROVE} + \text{DEVELOP} + \text{VACCINE} \cdot \text{COVERAGE} \cdot \text{COHORT} + \text{STAND.POP} \cdot \text{VECTORE}.$$

Appendix 14C. Numerical Values of Input Parameters

Parameter values are listed alphabetically below. For each parameter, we give the best estimate and the basis of that estimate. If no units are shown, the parameter is a pure dimensionless number. Values are shown in the form in which they are entered into the model. Thus value of CLINICAL below (16 percent) is shown as the decimal share 0.16.

CASES: 52,400 dengue infections in standard population per year. We estimated two infections per person per lifetime. Thus, CASES equals two times COHORT. Although a dengue infection confers immunity to the type of dengue virus which caused the infection, the person is still at risk of the remaining three of the four types of dengue virus. This is a long-term average level. During the 1981 dengue outbreak, Cuba (with a population of 10 million persons) had 2.36 million infections (based on serological data), or an infection rate of 236,000 per million population (Guzman and others 1990). Epidemics result from a buildup of susceptible persons. The long-term rate for CASES is about one-fifth of the Cuban rate.

CLINICAL: 0.16. This share is based on clinical data for DHF/DSS in children from Thailand (Halstead 1980b).

COHORT: 26,200 persons born per year in the standard population. The birth cohort size is the weighted average of the crude birth rate in the countries at risk of dengue. This was calculated as a weighted average of the crude birth rate per 1,000 population in countries with at least 1 million persons, based on data (generally for 1988) in the *World Development Report* (World Bank 1990). The value of this parameter corresponds to a crude birth rate of 26.2 per 1,000 population per year.

COVERAGE: 0.73. This is the overall coverage of DPT-3 among one-year-old children in developing countries at risk of dengue in 1987–88 (Grant 1990). If and when a dengue vaccine is developed, it will probably be offered to children through the delivery mechanism of the Expanded Programme on Immunization.

DEVELOP: $2,488. According to a study by the Institute of Medicine, Vaccine Development (1986), the cost of research and development to try to produce a useful dengue vaccine was estimated at $25 million; the probability of success was 0.75; when estimates were compiled in approximately 1985, twelve years were then thought to be required to license and adopt the vaccine. That is, the projected target year was 1997. During the past decade, researchers in Thailand, who have received about $5 million in external support from the Rockefeller Foundation and the Italian government, and the equivalent of several million dollars of in-kind support from the Thai government, have now produced a tetravalent vaccine in the laboratory and tested it successfully on 200 volunteers. (Replication of this research in an industrial country today would have cost about $100 million.) Final development, full-scale testing in humans, and development of production methods and capacity remain. These steps are estimated to require a further investment of $25 million and require five more years from 1992. Thus, the target date remains 1997. Because the average age at death was six (as described below), there is an additional five-year delay from administration of the first dose at age one until a death is potentially averted. Thus deaths will not be averted until ten years in the future (five for development plus five after administration).

In full use in a stable (long-term) situation, the vaccine would be offered to the birth cohort in all countries at risk of dengue. The population of countries at risk of dengue is 1,210 million people, or 1,210 times the standard-size calculation of 1 million people used in this analysis. To make costs commensurate with the timing of benefits, the future value of the expenditure needs to be calculated, at the time the vaccine would be in full use. Furthermore, because the success of research is not certain, the expenditure needs to be adjusted for the expected chance of success, now estimated at 90 percent. Because research and development is a capital cost, the expenditure must also be annualized over its expected useful life and rescaled for the birth cohort. We assign a twenty-year useful life to the current research effort, on the grounds that an improved vaccine would be available after that time. Several other important vaccines, such as measles and polio vaccines, have benefited from substantial improvements over this period. Thus, the cost per cohort was calculated as:

$$\$25{,}000{,}000 \cdot (1.03)^{(5+5)} / (1{,}210 \cdot 0.90 \cdot \text{annualizing factor}) = 2{,}488$$

where the annualizing factor is the present value of 1 for twenty years at 3 percent interest.

DURATION: 0.0148 year. A clinical episode of DHF/DSS is estimated to last nine days. This time counts the patient's inability to pursue his or her usual activities before, during, and after treatment. This duration is slightly longer than Osani's (1983) estimate of six days for dengue fever and the policy of the Brazilian social security system, which allows a worker seven days of authorized disability for a case of dengue fever (Kiela, personal communication, Everardo Chagas Hospital, Rio de Janiero, July, 1989). As Brazil then had virtually no DHF, the mean duration should be lower than in areas in which this complication occurred widely. The ill person has a fever, severe aches, and is generally prevented from working or carrying out his or her usual activity. Except for the minority of cases that progress to DHF/DSS, the victim can remain at home and is conscious but feels extremely uncomfortable. In cases that progress to hemorrhagic fever, the patient may be in shock for part of the illness. We have assigned a quality level of 0.4 to this acute illness on a scale where 0 denotes death and 1 perfect health. Thus, the morbidity loss is converted to an annual equivalent as $9/365 \cdot (1 - 0.4)$.

FATAL: 0.058. This rate was the case-fatality rate of DSS cases in Thailand in 1958–65, before good treatment became available (Halstead 1980a). On the basis of 158 deaths in 116,000 hospitalized patients, Cuba's case-fatality rate in hospitalized cases was 0.0014 during its 1981 dengue epidemic (Kouri and others 1987). Cuba has a good health system, so its case-fatality rate should reflect the effect of SALVAGE. Undoubtedly, the hospitals included some cases that were not DHF/DSS.

IMPROVE: 5. This is the estimated ratio of costs in a referral specialty hospital to those in a typical secondary hospital.

SALVAGE: 0.917. This rate of salvage of hemorrhagic cases is based on experience in Thailand following improvement in hospital care. It is the reduction in the former case-fatality rate of 0.058 (see FATAL, above) to the rate in 1986–89 of 0.0048.

SHOCK.R: 0.0078. This is the average of the rates of DHF/DSS (corrected to include only cases meeting WHO criteria) in Thailand in 1962 and Cuba in the epidemic of 1981. Thailand's rate was 7.5 DHF/DSS per 1,000 persons, calculated from the experience at Children's Hospital (Halstead 1980b). Cuba's rate of 0.0080 is based on 20,000 DHF/DSS compared with 2,360,000 infections during the epidemic (Guzman and others 1990).

SHORTEN: 0.25. Good clinical management improves the DHF/DSS patient's rehydration, shortens the period of shock, reduces bleeding, and hastens return to normal function.

STAND.POP: 1,000,000 persons. The size of the standard population (total of all age groups). The population of one million was chosen for consistency in comparing dengue with other interventions. Any other convenient size could be chosen, but the value of COHORT would have to be modified accordingly.

TREAT: $200. The cost of treating one case of dengue hemorrhagic fever is based on $40 per hospital day (the average in Brazil) times five days (the average for Thailand) of hospital care per case of DHF/DSS.

VACCINE: $40.87. The vaccine is expected to require two doses; the first at age one and the second five years later. This schedule is expected to offer protection at least through the period of greatest risk, from infancy through youth, if not longer. Because the vaccine contains four antigens to protect against all four dengue types, it is relatively complex to produce. In the study on vaccine development for the developing world by the Institute of Medicine (1986), estimated possible dengue vaccine costs ranged from $12.00 to $48.00. We now estimate a cost per dose of $10.00 to $25.00 with a midpoint of $17.50 for the vaccine itself. In addition, administration of the first dose at age one was assumed to cost $0.50, because it could likely be given during the contact for another vaccine, such as measles. The second dose, at age six, was assumed to require a separate contact. Because this might be done on a mass basis in schools, however, the delivery cost could be modest. We estimate a cost for this contact of $2.50, which is consistent with the per contact costs found in cost studies of the Expanded Programme on Immunization if all doses are considered (Shepard and others 1986). The combined two-dose cost is:

$$(17.50 + 0.50) \cdot (1.03)^5 + (17.50 + 2.50) = 40.87.$$

VACC.EF: 0.95. The Bureau of Biologics standard for immunogenicity (and efficacy) of live-attenuated viral vaccines in the United States is 95 percent. Tetravalent dengue vaccine would not be released until it is at least that effective.

VCTRC.EF: 0.30. Areas with vigorous efforts at vector control appear to have avoided outbreaks of dengue fever, whereas such outbreaks appear to have occurred in areas that lacked such programs. For example, Venezuela suffered a DHF/DSS epidemic in 1989–90 after apparently lax control programs. The Brazilian state of São Paulo, which has had a well-organized dengue control program, including clean-up campaigns, has had minimal dengue cases. Puerto Rico's ongoing spraying programs have helped to prevent large epidemics, although dengue still continues on the island.

VCTRE.EF: 0.95. The efficacy is based on the success of the control program in Singapore, which combined environmental control (elimination of breeding sites), education, localized chemical fogging, a law prohibiting conditions for disease-bearing insects, and slum clearance. Prior to the establishment of a vector control unit, dengue epidemics occurred annually. In 1966, for example, 630 cases were reported and 24 persons died of DHF. In a small epidemic a decade later (1978), only 2 deaths were reported. If the cycle of five-year epidemics had continued, another epidemic would have occurred in 1983, but none happened (Chan 1985). Thus the control program reduced both the severity and frequency of dengue epidemics. Puerto Rico controlled dengue to low levels in 1973 when large numbers of workers were hired to clean up neighborhoods under the War on Poverty's Comprehensive Employment and Training Act.

VECTORC: $0.46. This per capita cost is the average of per capita costs of dengue control in 1988 in Brazil ($0.25) and Puerto Rico ($0.67) based on original field studies. Although environmental control was used occasionally in these two areas, both relied primarily on chemical control during this year, especially spraying of streets and placement of abate or temefos in places where water collects.

VECTORE: $2.25. In the Singapore program, described above (Chan 1985), the cost was approximately $3.00 per capita. Environmental vector control not only reduces the risk of dengue but also reduces the population of *Culex* mosquitoes, whose bite is itchy and annoying. Because the dengue-carrying *Aedes aegypti* mosquitoes are smaller, their bite is less noticeable. Thus, the cost of effective vector control needs to be allocated between dengue and control of nuisance mosquitoes. To perform this calculation, we obtained figures from New Orleans, Louisiana, a city known to spend public funds on control of nuisance mosquitoes.

The expenditure ($1 million) and denominator (500,000 persons) in New Orleans give a per capita expenditure of $2.00 We interpret this amount as a revealed preference of willingness to pay for control of nuisance mosquitoes. In trying to extrapolate this result to Singapore, we assumed that this expenditure would be slightly income elastic, as is health expenditure generally. Assuming an income elasticity of 0.3 and using the fact that Singapore's per capita income ($7,500) is half that of New Orleans, we estimate that the per capita willingness to pay for control of nuisance mosquitoes would be $0.75, or one-quarter of the total per capita spending on environmental vector control. Subtracting this amount leaves a per capita expenditure of $2.25 allocated to dengue control.

YEAR.D: 25.5 years. In Southeast Asia, where there are good data on the age distribution of dengue deaths (Halstead 1969), the average age at death was about six years, and we have used this age for all areas at risk of dengue. We calibrated a model life table to the areas at risk of dengue. The calibration was based on the model West life table, which best fit the weighted average life expectancy for areas at risk of dengue. The West table best describes an "average" mortality pattern, and it is recommended when "no reliable information on the age pattern of mortality is available" (Newell 1988, p. 138). The weighted average (based on countries with a population of one million or more at risk of dengue), was 66.3 years (World Bank 1990). This average was best fit by the Level 20 model table, which yields a life expectancy of 65.6 years. We estimated remaining discounted life expectancy at age 6 years, using a discount rate of 3 percent. This estimation used 5-year age intervals beyond age 10, with a maximum at age 102.5 years.

Notes

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